

EXHIBIT A176

Perineal Talc Exposure and Subsequent Epithelial Ovarian Cancer: A Case-Control Study

CHEUNG WONG, MD, RONALD E. HEMPLING, MD, M. STEVEN PIVER, MD,
NACHIMUTHU NATARAJAN, MS, AND CURTIS J. METTLIN, PhD

Objective: To evaluate the role of talcum powder use as a risk factor for the development of epithelial ovarian cancer.

Methods: In a case-control study, 499 patients with epithelial ovarian cancer were frequency matched for age at diagnosis (± 5 years) with a control population of 755 patients. The odds ratio (OR) for the development of epithelial ovarian cancer was estimated using logistic regression analysis with adjustment for age at diagnosis, parity, oral contraceptive use, smoking history, family history of epithelial ovarian cancer, age at menarche, menopausal status, income, education, geographic location, history of tubal ligation, and previous hysterectomy.

Results: Two hundred twenty-one of 462 patients (47.8%) in the study population and 311 of 693 patients (44.9%) in the control population had ever used talcum powder (OR 0.92; 95% confidence interval [CI] 0.24, 3.62). A significant association between duration of talc use and development of epithelial ovarian cancer was not demonstrable for 1–9 years (OR 0.9; 95% CI 0.6, 1.5), for 10–19 years (OR 1.4; 95% CI 0.9, 2.2), or for more than 20 years (OR 0.9; 95% CI 0.6, 1.2). To eliminate the possible confounding variable of surgery for the management of ovarian cancer, we omitted 135 patients in the study population who underwent hysterectomy within 5 years of the diagnosis of ovarian cancer. Within this subgroup of patients, tubal ligation or hysterectomy among talc users still failed to demonstrate an increased risk for the development of ovarian cancer (OR 0.9; 95% CI 0.4, 2.2).

Conclusion: A significant association between the use of talcum powder and the risk of developing epithelial ovarian cancer is not demonstrable, even with prolonged exposure. (Obstet Gynecol 1999;93:372–6. © 1999 by The American College of Obstetricians and Gynecologists.)

Transvaginal exposure to talcum powder has been proposed as a risk factor for the development of epithelial ovarian cancer, not only because of the chemical

similarities between talcum powder and asbestos, but because the two chemical substances are often found together in mineral deposits. In 1967, the seminal work by Graham and Graham¹ demonstrated that intraperitoneal application of asbestos in guinea pigs and rabbits resulted in ovarian epithelial hyperplasia comparable to the histologic changes in early epithelial ovarian tumors observed in women. In 1971, Henderson et al² examined the ovarian tissue of 13 patients with epithelial ovarian cancer and reported that 75% of these tumors had talc particles embedded in the tissue. To further support the theory that retrograde flow of talc particles (after direct perineal application of talc) may result in deposition of particles on the ovary, Heller et al³ analyzed the ovaries of 24 women who underwent oophorectomies for benign ovarian neoplasms. Talcum powder was identified in all 24 patients. Twelve patients reported frequent perineal talc applications, but the remaining 12 denied ever using talc. Although histologic data appear to support the hypothesis that talcum powder applied to the perineum may migrate through retrograde flow, the role of talc as a risk factor for the development of ovarian cancer remains controversial.

The disparity among conclusions regarding the possible association between the use of talcum powder and the risk of ovarian cancer may lie in the fact that not all studies adjusted for the integrity of the genital tract. The integrity of a patient's genital tract is defined as intact when she has not undergone any of the following surgical procedures: salpingo-oophorectomy, bilateral tubal ligation, or hysterectomy (abdominal or vaginal). The purpose of the current study was to evaluate the use of talcum powder as a risk factor for the development of ovarian cancer in an analysis that includes the duration of use and the integrity of the genital tract.

From the Departments of Gynecologic Oncology and Cancer Control and Epidemiology, Roswell Park Cancer Institute, Buffalo, New York.

Materials and Methods

The application of talcum powder to the genital region among 499 patients with epithelial ovarian cancer treated at the Roswell Park Cancer Institute from October 1982 through October 1995 was compared with the application of talcum powder to the genital region among 755 female patients treated for nongynecologic malignancies during the same period. The case and control populations were frequency matched for age at diagnosis (± 5 years). Information regarding all patients was extracted from a database compiled from a self-administered questionnaire provided to the patients as a part of the enrollment process at our institute since 1953. The current document, in use since 1982, contains 44 items that pertain to the women's medical and social histories, including parity, menstrual history, use of exogenous hormones, contraceptive history, and personal hygiene. Additional information (besides the 44 items) regarding the patient's medical, social, family, dietary, and occupational histories is available and can be evaluated as potential confounding variables.

The diagnosis of each patient in the study population and in the control population was determined by reference to the Roswell Park Tumor Registry. Patients in the study population were coded with the International Classification of Diseases for Oncology, 1st ed. (ICD-O) code 8010/3 C56.9. The control population was randomly selected from the Roswell Park Tumor Registry. The pool of eligible patients was large enough to select 1.5 control patients for each patient in the study population. The control population consisted of 326 patients (43.3%) with colorectal cancer (ICD-O 8140/3 C16.0–C16.9), 23 patients (3.0%) with stomach cancer (ICD-O 8140/3 C16.0–C16.9), 11 patients (1.5%) with malignancy of the small intestine (ICD-O 8140/3 C17.0–C17.9), 134 patients (17.7%) with leukemia (ICD-O 9800/3-9940/3 C42.1), and 261 patients (34.5%) with malignancies of the skin (ICD-O C44.0–C44.9).

The odds ratio (OR) for the development of epithelial ovarian cancer was estimated using multiple logistic regression analysis with adjustment for oral contraceptive (OC) use, smoking history, family history of epithelial ovarian cancer, age at menarche, menopausal status, income, education, geographic location, and history of tubal ligation or hysterectomy. Among the study population, ORs were determined also to evaluate an association between histologic subtypes of epithelial ovarian cancer and the use of talcum powder, the duration of use of talcum powder and the risk for the development of ovarian cancer, and interruption of the continuity of the reproductive tract by either tubal ligation or hysterectomy and the risk of epithelial ovarian cancer. Data were analyzed using SPSS for

Table 1. Patient Characteristics

Characteristic	Cases (n = 499)	Controls (n = 755)	P
Mean age (y)	54.9	54.9	NS
Age at menarche (y)	12.8	12.8	NS
Age at menopause (y)	45.2	45.7	NS
Family history of ovarian cancer			
No	460 (92.2%)	735 (97.4%)	<.001
Yes	39 (7.8%)	20 (2.6%)	
Location			
Erie and Niagara counties	165 (33.3%)	392 (51.8%)	<.001
All others	331 (66.6%)	354 (46.9%)	
Unknown	3 (0.1%)	9 (1.3%)	
Parity			
0	105 (21.0%)	112 (14.8%)	.02
1–2	74 (14.8%)	107 (14.1%)	
3–4	200 (40.0%)	350 (46.4%)	
≥ 5	120 (24.0%)	186 (24.6%)	
Oral contraceptive use			
No	346 (69.3%)	507 (67.2%)	NS
Yes	148 (29.7%)	236 (31.2%)	
Unknown	5 (1.0%)	12 (1.6%)	
Race			
Black	6 (1.2%)	21 (2.8%)	NS
White	488 (97.8%)	732 (97.0%)	
Other	5 (1.0%)	2 (0.2%)	
Education			
Up to high school	262 (52.5%)	439 (58.2%)	.039
College	237 (47.5%)	316 (41.8%)	
Income			
<\$16,000	175 (35.1%)	314 (41.7%)	.013
\$16,000–\$24,999	133 (26.7%)	157 (20.8%)	
\geq \$25,000	191 (38.2%)	272 (37.5%)	

NS = not significant.

Windows, Advanced Professional Release 7.5-1997 (SPSS Inc., Chicago, IL).

Results

Characteristics of both the cases and controls are outlined in Table 1. A significantly ($P = .039$) greater proportion of patients in the study population attended college as compared with the control population, and a significantly ($P = .013$) greater proportion of patients in the control population had an annual income of less than \$16,000. Furthermore, a significantly ($P < .001$) greater proportion of patients in the study population (7.8%) had a family history of ovarian cancer than did patients in the control population (2.6%). A significantly ($P < .001$) greater proportion of patients in the control population lived in the counties immediately surrounding our facility compared with patients in the study population. Patients in the control population had significantly ($P = .02$) more children than did patients in the study population.

Information regarding the use of talc was retrievable

Table 2. Talc Use by Site: Odds Ratios and 95% Confidence Intervals

Site	Controls	Cases	OR* (95% CI)
Never used	382 (55.1%)	241 (52.2%)	1.0
Sanitary napkin	20 (2.9%)	13 (2.8%)	0.9 (0.4, 2.0)
Genital or thigh area	223 (32.2%)	157 (34.0%)	1.0 (0.8, 1.3)
Both	68 (9.8%)	51 (11.0%)	1.1 (0.7, 1.7)

OR = odds ratio; CI = confidence interval.

* Adjusted for parity, oral contraceptive use, smoking history, family history of epithelial ovarian cancer, age at menarche, menopausal status, income, education, geographic location, and history of tubal ligation or hysterectomy.

from the questionnaires of 462 patients in the study population and 693 patients in the control population. Thirty-seven patients in the study population and 62 patients in the control population failed to respond to the question regarding talc use. Among the cases, 47.8% (221 of 462) had ever used talc; 44.9% (311 of 693) of the controls had ever used talc ($P = .323$). Application of talc by site was similar in both groups: 3% of cases and controls applied talc on sanitary napkins, 34% of cases and 32.2% of controls applied talc on the genital or thigh area, and 11% of cases and 9.8% of controls applied talc to both sanitary napkins and the genital or thigh area. The adjusted OR did not demonstrate any increased risk for the development of ovarian cancer attributable to the method of talc application (Table 2).

Thirty-two patients from the case population and 39 patients from the control population did not recall the duration of talc use (Table 3). The mean duration of use was 22 years among patients in the control population and 21 years among patients in the study population. Both groups of women had used talc for a comparable period of time: 9.1% of cases and 9.3% of controls used talc for 1–9 years; 11.4% of cases and 7.6% of controls used talc for 10–19 years; and 23.5% of cases and 24.6% of controls used talc for more than 20 years. Among the study population, a significant association between the duration of talc use and the development of epithelial ovarian cancer was not demonstrable for 1–9 years (OR

0.9; 95% CI 0.6, 1.5), 10–19 years (OR 1.4; 95% CI 0.9, 2.2), or more than 20 years (OR 0.9; 95% CI 0.6, 1.2).

Among patients in the study population who had ever applied talcum powder to the perineum or to sanitary napkins, 136 patients (61.6%) had papillary serous cystadenocarcinoma, 21 patients (9.5%) had endometrioid carcinoma, 11 patients (5.0%) had mucinous adenocarcinoma, 12 patients (5.4%) had clear cell adenocarcinoma, and 41 patients (18.6%) had undifferentiated carcinoma. A significant association between the use of talcum powder and a specific histologic subtype of epithelial ovarian cancer was not demonstrable for serous cystadenocarcinoma (OR 1.2; 95% CI 0.7, 2.1), endometrioid carcinoma (OR 1.4; 95% CI 0.7, 2.7), mucinous adenocarcinoma (OR 1.5; 95% CI 0.6, 4.0), clear cell adenocarcinoma (OR 1.6; 95% CI 0.6, 4.3), or undifferentiated carcinoma (OR 1.0; 95% CI 0.6, 1.6).

To assess the impact of surgical interruption of the genital tract as a possible confounding variable, we evaluated the association between ovarian cancer and the use of talcum powder among patients in the study population who had not undergone any interruption of the genital tract compared with those in the study population who had undergone tubal ligation or hysterectomy. Among the cases, 267 patients (53.5%) had not had tubal ligation or hysterectomy, whereas 45.3% (226 patients) had undergone previously tubal ligation or hysterectomy. Of these 226 patients, 59.7% (135 patients) had a hysterectomy within 5 years of being diagnosed with ovarian cancer. Six women in the study group did not answer the question regarding history of tubal ligation or hysterectomy. There was no significant difference in the risk of developing ovarian cancer among patients in the study population with no history of genital tract interruption (OR 1.2; 95% CI 0.8, 1.6) and those with a history of tubal ligation or hysterectomy (OR 0.8; 95% CI 0.5, 1.2). To eliminate the possible confounding variable of surgery for the management of ovarian cancer, we excluded the 135 patients in the study population who had undergone hysterectomy within 5 years of the diagnosis of ovarian cancer. Within this subgroup of patients, tubal ligation or hysterectomy among talc users still failed to demonstrate that the use of talc significantly increased the risk of ovarian cancer (OR 0.9; 95% CI 0.4, 2.2) (Table 4). Multiple logistic regression analysis adjusted for age at diagnosis, parity, OC use, smoking history, family history of epithelial ovarian cancer, age at menarche, menopausal status, income, education, geographic location, and history of tubal ligation or hysterectomy failed to demonstrate any significant association between talc use and the development of ovarian cancer (OR 0.92; 95% CI 0.24, 3.62).

Table 3. Duration of Talc Use: Odds Ratios and 95% Confidence Intervals

Duration (y)	Controls*	Cases†	OR‡ (95% CI)
None	382 (58.4%)	241 (56.0%)	1.0
1–9	61 (9.3%)	39 (9.1%)	0.9 (0.6, 1.5)
10–19	50 (7.6%)	49 (11.4%)	1.4 (0.9, 2.2)
≥20	161 (24.6%)	101 (23.5%)	0.9 (0.6, 1.2)

Abbreviations as in Table 2.

* Thirty-nine patients did not recall duration of use.

† Thirty-two patients did not recall duration of use.

‡ Adjusted for factors stated in Table 2.

Table 4. Talc Users: Genital Tract Interruption and Risk of Ovarian Cancer

Operation	Talc use		OR* (95% CI)
	No	Yes	
No history of genital tract interruption			1.2 (0.8, 1.6)
Cases	130	121	
Controls	251	182	
History of tubal ligation or hysterectomy			0.8 (0.5, 1.2)
Cases	111	100	
Controls	131	130	
History of hysterectomy			0.9 (0.4, 2.2)
Cases	60	65	
Controls	14	21	

Abbreviations as in Table 2.

* Adjusted for factors stated in Table 2.

Discussion

The current study fails to demonstrate an association between the use of perineal talcum powder and a significant increase in the risk of epithelial ovarian cancer. These findings are at variance with a meta-analytic report by Gross and Berg,⁴ which demonstrated a modest increase in the risk of epithelial ovarian cancer among patients who had ever used talc. In an analysis of ten epidemiologic studies, Gross and Berg⁴ calculated an adjusted OR of 1.29 (95% CI 1.02, 1.63). Similarly, in a population-based case-control study, Harlow et al⁵ noted an increased risk (OR 1.57; 95% CI 1.0, 2.1) for the development of ovarian cancer among patients who had ever used talcum powder. This study, however, failed to adjust for OC use and family history of ovarian cancer. Moreover, 28% of the patients in that study population⁵ had borderline ovarian tumors; many investigators believe that this histopathologic entity differs substantially in pathogenesis and clinical course from invasive epithelial ovarian cancer. Despite these limitations, Harlow et al⁵ performed a meta-analytic calculation that described a modest association between the development of ovarian cancer and perineal talc use (crude OR 1.3; 95% CI 1.1, 1.6).

The results of the current study also differ from those reported by Cramer et al.⁶ These researchers reported a near doubling of risk for the development of epithelial ovarian cancer among talc users (relative risk [RR] 1.92; 95% CI 1.27, 2.89). However, calculation of risk in this study was adjusted only for parity and menopausal status. In a population-based case-control study by Cook et al⁷ that reported an adjusted RR of 1.5 (95% CI 1.1, 2.0), these researchers failed to demonstrate a trend in the OR with an increasing number of perineal applications. Important differences exist in the design of our study and that of Cook et al.⁷ Failure to adjust for a

family history of ovarian cancer is a potential limitation in the study by Cook et al⁷ because 26.9% of patients in the study population and 52.1% of the control population were less than 44 years of age (women diagnosed with ovarian cancer before the age of 45 may have a strong genetic predisposition for this disease). Furthermore, in the study by Cook et al,⁷ 79 patients (25.2%) in the study population were diagnosed with borderline epithelial ovarian tumor, a histologic entity that may have a different clinical course than invasive epithelial ovarian cancer.

The results of the current report do, however, support the conclusions of three hospital-based, case-control studies that failed to establish a significant association between the use of talc and an increased risk of epithelial ovarian cancer: Booth et al⁸ (RR 1.2; 95% CI 0.92, 1.8), Rosenblatt et al⁹ (RR 0.8; 95% CI 0.27, 2.63), and Tzonou et al¹⁰ (RR 1.05; 95% CI 0.38, 3.98). In a letter to the editor, Hartge et al (Hartge P, Hoover R, Leshner LP, McGowan L. Talc and ovarian cancer. JAMA 1983;250:1844) estimated the RR of ovarian cancer among talc users to be 0.7 (95% CI 0.4, 1.1). Additionally, in a collaborative review of hospital- and population-based case-control studies, Whittemore et al¹¹ failed to confirm a significantly altered risk of epithelial ovarian cancer (RR 1.4; 95% CI 0.98, 1.89) among patients who had applied talcum powder to the perineum.

Duration of exposure and the integrity of the female genital tract are crucial issues in the role of talc exposure as a risk factor for the development of epithelial ovarian cancer. Harlow et al⁵ argued that a 70% increase in the risk of ovarian cancer was evident among patients whose exposure to talc exceeded 10,000 applications (equivalent to 30 years of exposure) despite an intact genital tract and normal cyclic ovarian function. These calculations, although intriguing, should be interpreted with caution because they are based on a population of 38 patients, and a test for trend fails to achieve statistical significance ($P = .77$). Whittemore et al¹¹ observed a similar lack of significance for a trend in the duration of exposure. These researchers demonstrated no significant association between increased ovarian cancer risk and prolonged talc exposure (RR 1.3; 95% CI 0.88, 1.92). Moreover, when the population described by Whittemore et al¹¹ was stratified based on surgical sterilization and the use of talc, no significant association was observed between the integrity of the genital tract or talc exposure and an increased risk for the development of ovarian cancer. Data from the current study support the findings of Whittemore et al¹¹ because they demonstrate no significant increase in the risk of epithelial ovarian cancer among patients whose exposure to perineal talc exceeded 20 years, even in the presence of an intact genital tract.

Some significant differences between the study population and the control population were observed in the current study; these differences are in agreement with several epidemiologic studies that evaluated risk factors for the development of ovarian cancer.^{5,12-14} In the current study, patients with ovarian cancer acquired a higher level of education ($P = .039$) and higher income ($P = .013$) than the control population; patients in the control population had more children ($P = .02$) than in the study population. A greater proportion of the study group had a significant ($P < .001$) family history of ovarian cancer and lived remote from our institute. The reason may be that Roswell Park Cancer Institute has a referral center, the Gilda Radner Familial Ovarian Cancer Registry, for patients with an apparent genetic predisposition for the development of ovarian cancer. Overall, adjustment for these confounding variables in a multiple logistic regression model failed to demonstrate any significant association (OR 0.92; 95% CI 0.24, 3.62) between the use of talcum powder and the development of ovarian cancer.

Two potential weaknesses of this study should be addressed. First, as with any retrospective study using data collected from the patient's recall of events, potential ascertainment and recall bias may exist. To diminish ascertainment and recall bias, we asked patients to complete a 13-page questionnaire, which contains items pertaining to their medical, social, dietary, and occupational histories; no particular emphasis is placed on any of the items. Second, condoms and diaphragms are potential sources of talc exposure. The questionnaire asks patients whether they have ever used condoms or diaphragms as contraceptive methods; however, this questionnaire does not ask about the frequency or duration of such usage, whether lubricated or nonlubricated condoms were used, or whether talc was ever applied to the diaphragm. Consequently, the current study is limited to the use of talc on the perineum or sanitary napkins and does not address potential talc exposure from condom or diaphragm use.

The results of the current study fail to support the hypothesis that talcum powder usage is associated with the development of epithelial ovarian cancer, regardless of the duration of use and the integrity of the female genital tract.

References

1. Graham J, Graham R. Ovarian cancer and asbestos. *Environ Res* 1967;1:115-28.
2. Henderson WJ, Joslin CAF, Turnbull AC, Griffiths K. Talc and carcinoma of the ovary and cervix. *J Obstet Gynaecol Br Commonw* 1971;78:266-72.
3. Heller DS, Westhoff C, Gordon RE, Katz N. The relationship between perineal cosmetic talc usage and ovarian talc particle burden. *Am J Obstet Gynecol* 1996;174:1507-10.
4. Gross AJ, Berg PH. A meta-analytical approach examining the potential relationship between talc exposure and ovarian cancer. *J Expo Anal Environ Epidemiol* 1995;5:181-95.
5. Harlow BL, Cramer DW, Bell DA, Welch WR. Perineal exposure to talc and ovarian cancer risk. *Obstet Gynecol* 1992;80:19-26.
6. Cramer DW, Welch WR, Scully RE, Wojciechowski CA. Ovarian cancer and talc. *Cancer* 1982;50:372-6.
7. Cook LS, Kamb ML, Weiss NS. Perineal powder exposure and the risk of ovarian cancer. *Am J Epidemiol* 1997;145:459-65.
8. Booth M, Beral V, Smith P. Risk factors for ovarian cancer: A case-control study. *Br J Cancer* 1989;60:592-8.
9. Rosenblatt KA, Szklo M, Rosenshein NB. Mineral fiber exposure and the development of ovarian cancer. *Gynecol Oncol* 1992;45:20-5.
10. Tzonou A, Polychronopoulou A, Hsieh CC, Rebelakos A, Karakatsani A, Trichopoulos D. Hair dyes, analgesics, tranquilizers and perineal talc applications as risk factor for ovarian cancer. *Int J Cancer* 1993;55:408-10.
11. Whittemore AS, Wu ML, Paffenbarger RS, Sarles DL, Kampert JB, Grosser S, et al. Personal and environmental characteristics related to epithelial ovarian cancer. *Am J Epidemiol* 1988;128:1228-40.
12. Rodriguez C, Calle EE, Coates RJ, Miracle-McMahill HL, Thun MJ, Heath CW Jr. Estrogen replacement therapy and fatal ovarian cancer. *Am J Epidemiol* 1995;141:828-35.
13. Whittemore AS, Harris R, Itnyre J, and the Collaboration Ovarian Cancer Group. Characteristics relating to ovarian cancer risks: Collaborative analysis of 12 US case-control studies. *Am J Epidemiol* 1992;136:1184-203.
14. Shu OS, Gao YT, Yua JM, Ziegler RG, Brinton LA. Dietary factors in epithelial ovarian cancer. *Br J Cancer* 1989;1:92-6.

Address reprint requests to:
M. Steven Piver, MD
Roswell Park Cancer Institute
Elm and Carlton Streets
Buffalo, NY 14263

Received May 26, 1998.

Received in revised form August 27, 1998.

Accepted September 3, 1998.

Copyright © 1999 by The American College of Obstetricians and Gynecologists. Published by Elsevier Science Inc.